## REMARKS

Claims 1-3 and 6-9 are pending after entry of this paper. Claims 1-3 and 6-8 have been rejected and claims 6-8 have been objected. Claims 4-5 were cancelled in the preliminary amendment without prejudice. Claims 1-3 and 6-8 have been amended and claim 9 has been added as a new claim. Support may be found throughout the instant specification.

Claim 1 has been amended to describe the FcγRIIB gene-deficient mouse as being "homozygous." This claim has also been amended by rearranging the placement of several terms and by deleting other terms for clarification.

Claim 2 has been amended to depend from claim 1.

Claim 3 has been amended to include the word "model" and also to include the term "elevated levels of antibody titer against GQ1b."

Claim 6 has been amended to include the term "and/or Fisher syndrome" and has also been amended to solely depend from claim 3.

Claim 7 has been amended to solely depend from claim 3.

Claim 8 has been amended to include the term "and/or Fisher syndrome" and has been modified to solely depend from claim 6.

Claim 9 has been added as a new claim to incorporate the subject matter of original claim 8.

No new matter has been introduced by these amendments. Support may be found throughout the claims and specification as originally filed, for example, in paragraphs 7-8, 16, 22-23. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

**Response to Claim Objections**

Claims 6-8 are objected under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. Therefore, claims 6-8 have been amended to become singly dependent claims. Claim 9 has been added as a new claim in order to incorporate the claim dependency from claim 7 as originally claimed in claim 8.

No new matter has been introduced by these amendments. Support for these amendments can be found in the original claims and throughout the instant specification. Applicants respectfully request reconsideration and withdrawal of the claim objections in view of these amendments.

**Response to Claim Rejections under 35 U.S.C. §112, First Paragraph**

Claims 1-3 were rejected under 35 U.S.C. §112, first paragraph for allegedly not providing enablement for a model of Guillain-Barré syndrome (GBS) or Fisher syndrome or deficiency of the FcγRIIB gene or any other "mouse" showing the phenotype as claimed (*See* the Official Action dated December 5, 2006- page 3). Applicants respectfully disagree with the Examiner's contention.

The Examiner specifically contends that the recited "claims embrace immunizing homozygous as well as heterozygous FcγRIIB gene deficient mouse." (Office Action- page 4). Applicants respectfully disagree and traverse this contention. However, in order to expedite prosecution and solely for the advancement of the instant application, applicants have amended the claim to read "a homozygous FcγRIIB gene deficient mouse." Support for the amendment

can be found in paragraphs 7-8, 16, 22-23 of the instant specification. Applicants believe that this amendment addresses the Examiner's concerns.

Applicants also traverse the Examiner's contention that it is "apparent that any other genetic disruption including substitution or substitution of other exons will not result in the same phenotype." (Office Action – page 6). MPEP §2164.01 states that a specification only needs to provide "sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." Therefore, applicants do not need to demonstrate every gene knock out method. This technology is well-known in the art, therefore one of ordinary skill in the art would be able to make and use the invention from the description in the instant specification and with what is commonly known in the art.

On page 7 of the Official Action, the Examiner cites a reference by Holschneider, et al. in order to contend that deletion of an individual gene may cause "phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes." The Examiner also states that "it is not apparent how [a] skilled artisan without undue experimentation, practices [a] method as contemplated by the instant claims particularly given the unpredictability of the resulting phenotype of a mouse due to deletion of gene." Applicants respectfully disagree with and traverse the Examiner's contention.

As described in the instant specification, the FcγRIIB gene deficient mouse immunized with GQ1b ganglioside clearly displays a distinct phenotypic response compared to a wild-type mouse, namely paralysis of the tail and hind legs and elevated level of antibody titer against GQ1b. Support for this is also seen in Figures 1-3 of the specification. Therefore, as demonstrated, there is a distinct and predictable phenotype that results from a FcγRIIB gene-deficient mouse immunized with GQ1b ganglioside. It is further noted that the Holschneider, et

al. reference also mentions that "conventional knock-outs may help us better understand the plasticity of the nervous system and its various potential compensatory mechanisms. In some cases such studies may elucidate related proteins or pathways whose existence or functions were previously masked" (page 517, right column, last paragraph). Holschneider, et al. do not discredit the use and teachings of all types of conventional knock-outs, contrary to the Examiner's argument. Applicants respectfully request reconsideration of this argument.

The Examiner further contends that claims 2 and 3 as written are broad in scope and do not provide evidence that the claimed mouse shows characteristics consistent with other symptoms of GBS or Fisher syndrome without undue experimentation. The Examiner also argues that claim 2 can encompass any mouse showing a phenotype consistent with GBS or Fisher syndrome. Applicants respectfully disagree with the Examiner's contentions. However, in order to expedite prosecution and solely for the advancement of the instant application, applicants have amended claims 2 and 3 to depend from claim 1 and claim 1 or 2, respectively. Furthermore, the applicants have amended claim 3 by adding the symptom "elevated level of antibody titer against GQ1b." Support for the amendment to claim 3 can be found on page 14, paragraph 27 of the instant specification. Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph to claims 1-3 for the above reasons and in view of the aforementioned amendments.

**Response to Rejections under 35 U.S.C. §112-2nd Paragraph**

Claims 1-3 and 6-8 have been rejected under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the subject matter which the applicants regard as their invention. Applicants respectfully disagree.

Claim 1 has specifically been rejected as being indefinite to the extent that the preamble is not consistent with the rest of the body of the claim. Applicants have amended the syntax of the claim in order to expedite prosecution and solely for the advancement of the instant application. Specifically, applicants have changed the phrase "can be obtained by..." to now read, "obtained by...." Applicants have also amended the wording "FcγRIIB gene function is deficient in its chromosome" to now read "a homozygous FcγRIIB gene deficient mouse". No new matter has been introduced by these amendments. Support may be found throughout the instant specification and claims. Applicants believe that these amendments address the Examiner's concerns.

Furthermore, claim 3 has been rejected for allegedly being vague as to how and under what conditions the mouse develops peripheral neuropathy. Applicants disagree with the Examiner's contention. Applicants believe that amending claim 3 to depend on claim 1 or amended claim 2 renders this argument moot. Therefore, the conditions of claim 1, namely, immunizing a homozygous FcγRIIB gene deficient mouse with GQ1b ganglioside, apply to claim 3. Applicants respectfully request reconsideration and withdrawal of the rejection in view of the amendments.

Moreover, claim 3 has been rejected for allegedly being unclear due to the limitation "according to". Applicant's disagree, however in order to expedite prosecution and

solely for the advancement of the instant application, claim 3 has been amended to make specific reference to the mouse model per the Examiner's suggestion.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph to claims 1-3 in view of the aforementioned amendments.

**Response to Rejections under 35 U.S.C. §102**

Claims 2-3 have been rejected under 35 U.S.C. §102(b) as being anticipated by Reinhard, et al. (*Adv. Exp. Med. Biol.*, 1996; 398:241-6). Applicants respectfully disagree.

According to MPEP §2131:

> A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The Reinhard reference cited by the Examiner describes a mouse which displays signs of encephalomyelitis (i.e., hind-limb paralysis, flaccid tail and loss of bladder control) following retroperitoneal, intradermal inoculation with HSV-1. Reinhard further evaluates the levels of quinolinic acid in response to HSV-1 inoculation. Guillain-Barré syndrome or Fisher syndrome are not mentioned or described in the cited reference. In fact, the authors describe an effect that resembles a different disease altogether, EAE, a mouse model for multiple sclerosis (Reinhard, page 244, first paragraph):

> The first neurological signs observed were consistent with spinal cord involvement and are reminiscent of experimental autoimmune encephalomyelitis (EAE). Indeed, in EAE, tissue [quinolinic acid] content was increased.

However, in order to expedite prosecution and solely for the purpose of allowance of the instant application, applicants have amended claims 2 and 3 to depend from claim 1 and claim 1 or 2, respectively. In addition, claim 3 has been amended to include the phenotype of "elevated levels of antibody titer against GQ1b." (Support for these amendments have already been discussed in preceding paragraphs). Therefore, the dependent claims incorporate all of the limitations of the claim(s) to which they refer. The Reinhard, et al. reference does not describe "a mouse model of Guillain-Barré syndrome obtained by immunizing a homozygous FcγRIIB gene deficient mouse with GQ1b ganglioside," nor does Reinhard, et al. describe the phenotype of "elevated levels of antibody titer against GQ1b," hence, Reinhard, et al. does not anticipate the claims. Reconsideration and withdrawal of the 35 U.S.C. §102(b) anticipation rejection to claims 1-3 are respectfully requested in view of the aforementioned arguments and amendments.

**Response to Rejections under 35 U.S.C. §103(a)**

Claims 1-3 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Takai et al. (*Nature*, 1996, 379, 346-348, IDS), in view of Yuki et al. (*Ann. Neurol.*, 2001, 49, 712-720), and further in view of Odaka et al. (*J. Neurol. Neurosurg. Psychiatry.*, 2001; 70(1): 50-5). Applicants respectfully disagree and traverse this contention.

According to the Examiner's contention, the Takai, et al. reference states that loss of the FcγRIIB gene in mice increases humoral and anaphylactic responses because the mice lack the ability to regulate antibodies in response to antigenic stimulation. The Examiner further contends that there would have been a reasonable expectation of success to use these mice for the purpose of studying GBS or Fisher syndrome in this application because Takai, et al. had already

described the advantage of using the FcγRIIB knockout mouse to study autoimmunity. As an initial matter, the Examiner assumes that all autoimmune diseases (or autoimmune disease models) operate by the same mechanism, namely, through the FcγRIIB inhibitory pathway. One skilled in the art understands that many different mechanisms exist for autoimmunity which may be unrelated to, and/or distinct from, FcγIIB deficiency. Therefore, the Examiner's argument that there was a reasonable expectation of success for using this mouse as a model for a different form of autoimmunity than what is disclosed in the reference is moot. Applicants also note that the Examiner admits that Takai, et al. does not teach immunization of the FcγRIIB deficient mice with ganglioside GQ1b (Office Action- page 13).

The Examiner combines Takai, et al. with Yuki et al. as disclosing a rabbit model immunized with either a mixture of bovine brain ganglioside (BBG) or GM1 individually as causing Guillain-Barré syndrome (GBS) characterized by limb weakness. The Examiner admits that the reference specifically states that the findings "have failed confirmation in rodents." (*See* Yuki et al., p. 712, second column). Hence, it is acknowledged that there has been a failure of others in the field to produce a mouse model for GBS or Fisher syndrome. Therefore, because attempts to immunize mice with ganglioside have previously failed, it is not obvious to one skilled in the art that immunizing mice with GQ1b ganglioside would induce GBS or Fisher syndrome in a wild-type or an FcγRIIB deficient mouse. Furthermore, Yuki, et al. immunize rabbits with either GM1 alone or a mixture of bovine brain ganglioside (BBG), including GM1, GD1a, GD1b, and GT1b. The Examiner admits that Yuki, et al. does not teach immunization with GQ1b (Office Action- page 14). In the Yuki, et al. reference, none of the reported animal subjects produced IgM or IgG antibody against GQ1b (table 2). Thus, in this study, the BBG mixture used for immunization did not result in a production of antibodies against GQ1b (i.e.,

there was no cross-reactivity between the mixture of gangliosides with GQ1b). Also, in the subjects that were immunized with the BBG mixture, the immune response was primarily directed against GM1, even though the mixture contained more GD1a (Yuki, et al., page 719, left column, last paragraph). This result argues for a case of non-obviousness since immunization with a mixture of ganglioside tends to result in a GM1 response over other gangliosides. Finally, Yuki, et al. specifically discusses GBS but does not discuss Fisher syndrome, which is a variant of GBS characterized by augmented expression of anti-GQ1b IgG.

The Examiner also combines Takai, et al. and Yuki, et al. with Odaka, et al. as an additional reference to argue *prima facie* obviousness. Specifically, the Examiner contends that Odaka, et al. discloses that patients with Miller Fisher syndrome and GBS had serum IgG antibody to GQ1b ganglioside during the acute phase of the illness. The Examiner admits that Odaka, et al. does not teach immunizing any mouse for a mouse model of GBS or Fisher syndrome. Additionally, the Examiner contends Odaka, et al. discloses that a single strain of *C. jejuni* that has several lipopolysaccharides bearing epitopes common to such gangliosides as GM1, GD1a, and GQ1b (Office Action- page 14). Okada's claim that *C. jejuni* has several lipopolysaccharides that bear epitopes common to such gangliosides as GM1, GD1a, and GQ1b (page 54, column 3, paragraph 3) were based on two separate references (references 39 and 40 cited in Okada, et al.). Upon further investigation, these references explain that *C. jejuni* have lipopolysaccharides which mimic GM1 and GD1a (reference 39, abstract) and GM1 (reference 40, abstract). These references, however, do not describe *C. jejuni* as mimicking the GQ1b ganglioside. As mentioned in the preceding paragraph, the rabbits disclosed in Yuki, et al. which were immunized with the BBG mixture (which included GM1 and GD1a) did not display an increase in anti-GQ1b IgG. Therefore, it would not have been obvious to one skilled in the art to

combine the Odaka, et al. and Yuki, et al. references to expect that immunizing an animal with any combination of ganglioside or *C. jejuni*-mimic ganglioside would result in an increased expression of anti-GQ1b IgG and in combination with Takai, et al., result in the claimed invention.

For the aforementioned reasons, the Examiner's case for *prima facie* obviousness is traversed. Applicants argue that it would not have been obvious to one skilled in the art to combine the cited references to expect successful results. The FcγRIIB deficient mouse can not be expected to be a successful model for all types of autoimmunity. Additionally, it would not have been expected that immunizing a mouse with gangliosides, individually or in combination, would result in a specific augmentation of anti-GQ1b IgG. The combination of cited references does not remedy the deficiencies of each of the cited references to result in the claimed mouse model of GBS. One skilled in the art has no motivation nor guidance to modify the teachings found in Takai, et al., Yuki, et al., and Odaki, et al. to produce a GBS mouse model obtained by immunizing a homozygous FcγRIIB gene deficient mouse with GQ1b ganglioside. The applicants respectfully request that the Examiner reconsider and withdraw the *prima facie* 35 U.S.C. §103(a) rejection to claims 1-3.

**Dependent Claims**

The applicants have not independently addressed all of the rejections of the dependent claims. The applicants submit that for at least similar reasons as to why independent claim 1, from which all of the dependent claims 2-3 and 6-9 depend, are believed allowable as discussed *supra*, the dependent claims are also allowable. The applicants however, reserve the

right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections be withdrawn.

## CONCLUSION

Based on the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

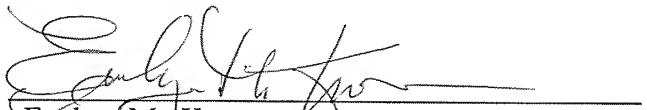
## AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4439-4032.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4439-4032.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: March 5, 2007

By: 
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